PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Clinical Features of Children With Screening-Identified Evidence of Celiac Disease

Edward J. Hoffenberg, Lisa M. Emery, Katherine J. Barriga, Fei Bao, Jennifer Taylor, George S. Eisenbarth, Joel E. Haas, Ronald J. Sokol, Iman Taki, Jill M. Norris and Marian Rewers

Pediatrics 2004;113;1254

Clinical Features of Children With Screening-Identified Evidence of Celiac Disease

Edward J. Hoffenberg, MD*; Lisa M. Emery, MSPH‡; Katherine J. Barriga, MSPH‡; Fei Bao§; Jennifer Taylor, MD§; George S. Eisenbarth, MD, PhD§; Joel E. Haas, MD‖; Ronald J. Sokol, MD*; Iman Taki, BS‡; Jill M. Norris, PhD‡; and Marian Rewers, MD, PhD‡§

ABSTRACT. *Objective.* **At-risk groups commonly undergo screening for autoantibodies associated with celiac disease (CD). However, the clinical significance of a positive test remains uncertain. The objective of this study was to evaluate growth and clinical features of children who test positive for an autoantibody associated with CD.**

Methods. **A case-control study of Denver area healthy infants and young children with and without CD autoantibodies was conducted. A cohort of HLA-characterized children were followed prospectively since birth for the development of immunoglobulin A antitissue transglutaminase autoantibodies (TG). Clinical evaluation, questionnaire, blood draw, and small bowel biopsy were performed. Growth and nutrition and frequency of positive responses were measured.**

Results. **Compared with 100 age- and gender-matched TG-negative controls, 18 TG-positive children, 5.5 ± 0.5 years of age, had a greater number of symptoms and lower *z* scores for weight-for-height and for body mass index. Responses that were independently associated with TG-positive status were irritability/lethargy, abdominal distention/gas, and difficulty with weight gain.**

Conclusions. **Screening-identified TG-positive children demonstrate mild alterations in growth and nutrition and report more symptoms than control subjects. Additional study is needed on the benefit and risk of identifying CD in at-risk groups. *Pediatrics* 2004;113: 1254–1259; *celiac disease, IgA, transglutaminase, children, body mass index, autoimmunity, screening.***

ABBREVIATIONS. CD, celiac disease; EMA, endomysial antibodies; TG, transglutaminase antibodies; IgA, immunoglobulin A; BMI, body mass index; OR, odds ratio; CI, confidence interval.

Evidence of celiac disease (CD) may be present in 1 in every 100 to 250 children,[1,2] adolescents,[3] and adults[4,5] in Europe and the United States.[6] Individuals who are identified by autoantibody screening as having evidence of CD autoimmunity have few, mild symptoms or no symptoms at all[7] and are identifiable only by screening. In symptomatic children with CD, clinical features include diarrhea, abdominal distention, failure to thrive, abdominal pain, and delayed puberty.[8] The 1990 European Society for Pediatric Gastroenterology and Nutrition (ESPGAN) criteria for the clinical diagnosis of CD require typical intestinal mucosa alterations plus a response to a strict gluten-free diet, such as resolution of histologic changes or of symptoms; the disappearance of autoantibodies is additional supportive evidence.[9] Recent reviews and consensus statements have reaffirmed these basic criteria.[8,10]

These expert consensus statements regard the presence of autoantibodies as helpful but not required for the clinical diagnosis of CD. In patients with symptomatic CD, the presence of circulating antiendomysial antibodies (anti-EMA) or antitissue transglutaminase antibodies (TG) is highly predictive (97%–100%) of biopsy changes of CD.[11,12] However, in screening programs of at-risk populations, these same autoantibodies (TG and EMA) may have a lower positive predictive value (75% to 85%) for biopsy evidence of CD, despite a similar genetic background as symptomatic patients.[7,13] Individuals who have evidence of "CD autoimmunity" but absent typical histologic changes[14] do not meet criteria for the clinical diagnosis of CD.[9]

Nevertheless, screening at-risk populations, such as those with type 1 diabetes, for CD-associated antibodies has become common despite a lack of information about the short- and long-term implications of screening-identified CD. For example, it is not known whether individuals with screening-identified CD (or celiac autoimmunity) have the same long-term risks as patients with symptomatic CD for osteoporosis,[15] lymphoma,[16] and nutritional deficiencies. In addition, efforts at case finding need to be tempered by the realization that only ~50% of individuals with CD follow a strict gluten-free diet.[8,17] Unfortunately, there are no tools to determine which individuals might benefit from early identification of CD and from early treatment with a gluten-free diet.

A prospective general population screening and follow-up study has been under way in Denver since 1993 in which a cohort of HLA-DRB1*03 characterized newborns have undergone serial testing for CD autoimmunity.[12] Children with repeatedly positive tests for TG have undergone clinical evaluation and small intestinal biopsy. The purpose of this article is to report the clinical features of the first 18 TG-

From the *Departments of Pediatrics, ‡Preventive Medicine and Biometrics, and ‖Pathology, §Barbara Davis Center for Childhood Diabetes, Children's Hospital, and the University of Colorado School of Medicine, Denver, Colorado.

Received for publication Mar 18, 2003; accepted Jul 7, 2003.

Reprint requests to (E.J.H.) B-290, 1056 E 19th Ave, Denver, CO 80218. E-mail: hoffenberg.edward@tchden.org

positive children in this cohort who have undergone clinical evaluation for CD and small intestinal biopsy.

METHODS

This report compares clinical features of 18 screening-identified TG-positive children with 100 age- and gender-similar TG control subjects. All children were born at Saint Joseph's Hospital (Denver, CO) and participated in a prospective study evaluating genetic and environmental risks for CD and type 1 diabetes.[18] The newborn population of Saint Joseph's Hospital was chosen because it was representative of the general population of Denver Metropolitan Area and included children who were classified by their mothers as non-Hispanic white (56%), Hispanic (30%), African American (7%), Asian American (2%), or biracial/other (5%).[19]

Among the 1234 families who participated in follow-up, 33 children have tested positive for TG. Of these, 18 have undergone repeated testing for TG, clinical evaluation, and small intestinal biopsy by a single pediatric gastroenterologist. The other 15 families either declined evaluation ($n = 3$) or are considering or awaiting clinical evaluation and biopsy ($n = 12$).

Control Group

For comparison with the children with celiac autoimmunity, 100 TG-negative children of similar age and gender from the same cohort of 1234 were chosen (ie, frequency matched). For comparison, information gathered from the questionnaire completed by telephone interview at 5 years of age was used.

HLA Genotype Screening

Genotypes were categorized as HLA-DR3/3 (homozygous), 3/x (heterozygous), or x/x (absent) on the basis of the number of copies of the DRB1*03 allele. The polymerase chain reaction–based genotype screening was performed by Roche Molecular Systems (Alameda, CA) and has been previously described in detail.[18]

Questionnaire

Families in follow-up completed an annual questionnaire to determine the presence or absence of 7 items associated with CD: abdominal pain, constipation, poor weight gain, irritability or lethargy, abdominal distention or gas, diarrhea, and short stature. The questionnaire was administered by a trained study coordinator during a telephone interview or by a single physician at the time of clinical evaluation. Therefore, questionnaire data are available from 3 time intervals: before development of TG-positive status, after knowledge of TG-positive status, and at clinical evaluation.

Autoantibody Assay

Immunoglobulin A (IgA) antibodies to TG were detected using a radioimmunoassay with in vitro transcribed and translated human transglutaminase cDNA.[20] Coded samples were tested in duplicate. All positive test results were confirmed by blinded duplicate sample testing. (Before 1998, EMA was used for screening; all EMA-positive samples were later confirmed also to be TG positive.)

Definition of Celiac Autoimmunity and Evidence of CD

Celiac autoimmunity (TG-positive) was defined as the persistence of TG autoantibodies on 2 consecutive occasions at least 6 months apart. Evidence of CD was defined as a positive test for TG plus histologic findings on intestinal biopsy, characterized by a Marsh score of 2 (enlarged crypts and increased numbers of intraepithelial lymphocytes) or 3 (any degree of villous atrophy).[13]

Intestinal Biopsy

Intestinal biopsy specimens were obtained initially with a Carey capsule (Wilson-Cook Medical, Inc, Winston-Salem, NC; $n = 4$) and then by upper gastrointestinal endoscopy ($n = 14$) with 2 to 4 specimens obtained from the descending duodenum. A single pathologist, unaware of clinical information, assessed the biopsy specimen according to the scoring system described by Marsh.[14]

IgA Deficiency Evaluation

In all children, IgA was measured using a nephelometric method (The Binding Site Limited, Birmingham, England). When IgA was low, IgG TG antibodies were measured.

Growth and Nutrition

Age- and gender-matched z scores [(value − mean value for gender and age) ÷ standard deviation] were obtained for height, weight, and body mass index (BMI) from a United States database available at www.cdc.gov/growthcharts.[21] World Health Organization reference data were used for arm circumference-for-age[22] and for height.[23]

Vitamin E and Zinc

Blood samples were obtained after an overnight fast at the time of small intestinal biopsy. Plasma was separated immediately after blood was drawn and was stored at −70°C. Plasma α tocopherol was measured by high-performance liquid chromatography.[24] Total lipids were measured using a colorimetric assay.[25] The ratio of α tocopherol to total lipids (mg/g) was used to assess accurately vitamin E status.[26] Fasting plasma zinc was measured by atomic absorption spectrophotometry.[27]

Statistical Methods

Fisher exact test was used for comparison of groups in which a 2×2 cell contained <5. The unpaired t test was used for comparison of z scores that have a normal distribution. Mann-Whitney test was used for comparison of TG-positive group before and at clinical evaluation. A 3×2 χ^2 test or Kruskal-Wallis test was used to compare the TG-positive group at the 3 time intervals. The Spearman test was used to assess correlations between histology score and nutritional variables. Logistic regression was performed using TG status as the outcome variable and the proportion reporting the presence of each item as the predictor. The "backward" option in SAS (SAS Institute, Cary, NC) was used to identify items independently associated with TG status. The Colorado Multiple Institutional Review Board for Human Research approved this study, and informed, written consent was obtained from parents or legal guardians.

RESULTS

The TG-positive and TG-negative groups were of similar ethnic, gender, and age distribution (Table 1). For the TG-positive group, the mean age at first positive TG test was 4.4 ± 1.2 years, and the mean age at clinical evaluation was 5.3 ± 1.5 years. Four children in the TG-negative group and none in the TG-positive group had low IgA levels. All 4 had negative tests for IgG TG.

Of the 18 TG-positive children, 13 (72%) had biopsy evidence of CD (Marsh 2 or 3 score), 2 showed increased intraepithelial lymphocytes (Marsh 1), and

TABLE 1. Demographic and Clinical Data for 18 Screening-Identified TG-Positive Children at Time of Clinical Evaluation and for 100 TG-Negative Age- and Gender-Similar Children

	TG-Positive ($n = 18$)	TG-Negative ($n = 100$)
Ethnicity		
Non-Hispanic white	15 (83%)	74%
Hispanic	3 (17%)	21%
Other	0	5%
Male:female	1:2	1:2
Age, y	5.3 ± 1.5	5.2 ± 0.1
Range	2.3–7.3	5.0–5.6
TG index (normal <0.05)	0.59 ± 0.53	<0.05

Data are mean ± standard deviation

TABLE 2. Relationship Between HLA Genotype and Histologic Findings From 18 Screening-Identified TG-Positive Children Who Underwent Small Intestinal Biopsy

HLA Genotype	Marsh Score				% With Histologic Evidence of CD
	0	1	2	3	
3/3	2	0	1	2	60% (3/5)
3/x	0	2	2	7	82% (9/11)
x/x	1	0	0	1	50% (1/2)

A Marsh score of 2 or 3 was considered histologic evidence of celiac disease.[14]

3 had normal biopsies (Marsh 0).[14] No relationship between number of copies of HLA-DR3 and biopsy score was evident (Table 2).

Compared with the TG-negative group, the TG-positive group had decreased *z* scores for weight-for-height (-0.3 ± 0.7 vs 0.3 ± 1; $P = .02$) and BMI (-0.3 ± 0.7 vs 0.4 ± 0.9; $P < .01$) but not weight- or height-for-age (Fig 1). The *z* scores for BMI and weight-for-height did not show any significant changes before or soon after development of TG seropositivity.

Additional anthropometric data obtained on the TG-positive group at the time of intestinal biopsy (mid-arm circumference and triceps skinfold) were compared with published age- and gender-matched normative data from the Third National Health and Nutrition Examination Survey of American children[28] and stratified by intestinal biopsy histology score. The TG-positive group had decreased *z* scores for mid-arm circumference (-0.66 ± 0.94) and for mid-arm muscle area (a measure of muscle mass; -0.53 ± 0.96).

All of the 18 TG-positive children had normal test results for aspartate aminotransferase and alanine aminotransferase ($n = 17$), vitamin E to total lipids ratio, and zinc. However, plasma zinc concentration correlated inversely with intestinal biopsy histology score ($r = -0.548$, $P = .03$).

Questionnaire information is summarized in Table 3. Before development of TG-positive status, the number of symptoms reported was similar to that of the TG-negative control group (0.2 ± 0.6 vs 0.3 ± 0.8; $P = .96$). However, after knowledge of TG-positive status, a greater number of items were reported (compared with TG-negative control subjects) at both the telephone interview (0.7 ± 0.8; $P = .001$) and the clinic visit (TG-positive: 2.4 ± 1.7; $P < .0001$). The time interval from the questionnaire completed be-

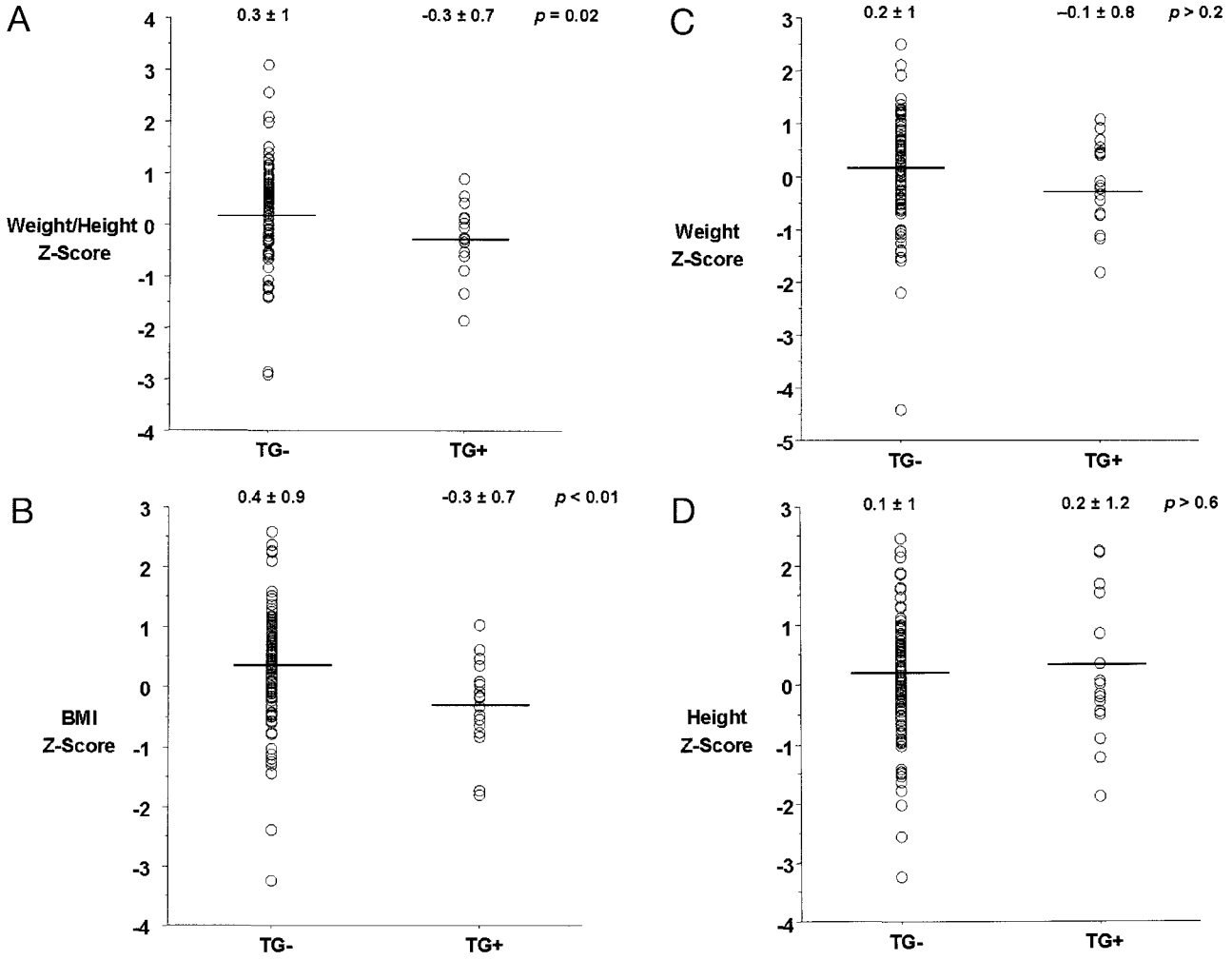

Fig 1. *Z* scores for weight-for-height (A), BMI (B), weight (C), and height (D) from 18 screening-identified TG-positive children and 100 TG-negative age- and gender-similar children.

TABLE 3. Questionnaire Data on 18 Screening-Identified TG-Positive Children and 100 TG-Negative Age- and Gender-Similar Children

	TG+ Group			TG-Control Group (n = 100)
	Before TG+ (n = 14)	After TG+ (n = 15)	Clinical Eval. (n = 18)	
Age (y [median, range])	3.1 (2.0–6.5)	4.2 (2.6–6.7)	5.3 (2.6–7.5)	5.2 (5.0–5.6)
No. of items*	0.2 ± 0.6	0.7 ± 0.8§	2.4 ± 1.7‖	0.3 ± 0.8
Frequency of items				
Abdominal pain*	0%	7%	39%‖	3%
Constipation†	0%	20%	33%‡	7%
Poor weight gain	7%	13%	28%§	3%
Irritability/lethargy	7%	13%	34%§	2%
Gassy/distended	7%	13%	22%‡	1%
Diarrhea	0%	7%	22%‡	1%
Short	0%	7%	11%	3%
None*	86%	60%	22%‖	87%

Before TG+ indicates most recent data before the first TG+ test; After TG+, data at time of first TG+ test; Clinical eval, data obtained at time of clinical evaluation by a pediatric gastroenterologist. Using logistic regression analysis, poor weight gain, irritability/lethargy, and gassy/distended were items found to be independent predictors of TG status. Mean ± standard deviation or median (range). Change over time in TG+ group: * $P \leq .01$, † $P \leq .05$.
TG+ at clinical evaluation compared with control: ‡ $P \leq .01$, § $P \leq .001$, ‖ $P \leq .0001$.

fore development of TG-positive status to that completed at clinical evaluation was 11 ± 12 months (range: 3-40 months).

Analysis of the 3 questionnaires obtained in the TG-positive group over time showed that the number of items reported increased significantly (Table 3). Specific items that increased significantly over time were abdominal pain and constipation. The number who reported 0 items present decreased over time from 86% to 60% and then to 22% ($P < .01$).

At the clinical evaluation, the most common items reported were abdominal pain (39%), irritability/lethargy (34%), and constipation (33%). In contrast, in the TG-negative group, the most common item was constipation (7%). Families from 2 TG-positive children were considering seeking medical attention for their child's symptoms.

In a logistic regression model, 3 items emerged as being independently associated with TG status: poor weight gain ($P < .04$; odds ratio [OR]: 7.5; 95% confidence interval [CI]: 1.2–48.8), irritability/lethargy ($P < .01$; OR: 17.8; 95% CI: 2.6–122.4), and distention/gas ($P < .001$; OR: 16.6; 95% CI: 3.2–87.6).

DISCUSSION

According to the Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition, major issues that are in need of investigation in CD include "knowledge of the natural history" and "the benefits of treating clinically silent cases."[29] Whether at-risk groups or entire populations should be screened and whether asymptomatic screening-identified patients with evidence of CD should be treated with a gluten-free diet have been debated.[30] We present data from a cohort of newborns who were followed prospectively over time that provides novel information concerning these issues.

The main finding in this study is of a mild alteration in body weight and body composition in screening-identified TG-positive children compared with control subjects. Children with evidence of CD had decreased z scores for weight-for-height, BMI, mid-arm circumference, and mid-arm muscle area. In cystic fibrosis, another disease associated with malabsorption and chronic inflammation, alterations in body composition are associated with increased inflammatory mediators.[31] Similar proinflammatory cytokines, including tumor necrosis factor[32] interferon-α,[33] interferon-γ,[32] and interleukin-18,[34] are increased in CD. Inflammatory mediators as well as malabsorption may have a role in alterations of body weight and body composition that we identified. This study did not evaluate inflammatory mediators.

A second finding was that intestinal biopsy histology score correlated inversely with plasma zinc concentration. Decreased concentrations of zinc and other micronutrients may be attributable to an acute-phase response[35] and reverses with treatment with a gluten-free diet.[36]

A third finding of this study is the increase in number of reported questionnaire items over time and the identification of 3 items in "asymptomatic" subjects associated with TG seropositivity: irritability/lethargy, distention/gas, and poor weight gain. Although the responses are compared with age- and gender-matched seronegative control children, the interpretation of this information should take into account the possible role of bias introduced by knowledge of TG status. The unique prospective nature of the study design allowed us to obtain questionnaire information before TG-positive status, as well as when the families were notified of TG-positive status, and again at the time of intestinal biopsy. This study was not designed to distinguish between the possible influences of parental knowledge of TG status, repeated questioning, and CD itself on the responses.

Information on the natural history of CD is timely because of a position statement supporting screening of at-risk groups.[37] However, we believe that caution is justified before recommending that children and adolescents, self-perceived as healthy, receive medical advice that they have a life-long disease that

should be treated with a strict gluten-free diet. Four areas need additional evaluation. First is determining whether screening-identified and clinically identified CD have similar outcomes. It is possible that some but not all individuals with screening-identified evidence of CD are at risk for clinical sequelae of untreated CD. Thus, a "splitting" as opposed to "lumping" approach may increase the benefit relative to risk relationship, as well as gain broader acceptance in the public and medical community.

The second area, related to the first, is the need to determine whether treatment before symptoms develop, as opposed to after, changes long-term outcome. This is of particular interest to those who care for individuals with type 1 diabetes, a population in which the prevalence of CD is between 4% and 10% and in whom instituting a strict gluten-free plus diabetic diet may be especially challenging.[38] Several small studies have not supported the hope that early treatment of CD would improve growth or diabetes control.[39–41]

The third area is whether the benefits of early diagnosis outweigh the harm. In older children and adolescents, the diagnosis of a chronic disease that requires significant diet alteration may have a negative impact on development.[42] No studies of "asymptomatic" children have evaluated the impact that the diagnosis of CD has on age-appropriate developmental tasks such as autonomy, sense of identity, and peer relationships. The patient with diabetes, now faced with 2 chronic diseases and a diabetic plus gluten-free diet, may be particularly affected. It is not surprising that ~50% of children and teens who receive a diagnosis of CD do not comply with a gluten-free diet.[41]

The fourth issue is the definition of CD. The ESPGAN criteria require a characteristic intestinal mucosal lesion plus a response to a gluten-free diet, with improvement of either histologic findings or symptoms.[9] The requirement for a response is often not fulfilled because demonstration of improvement in symptoms is a subjective outcome and resolution of the histologic lesion is not possible because of failure to comply with a strict gluten-free diet or because affected individuals are comfortable with the diagnosis and believe it unnecessary to repeat the biopsy. In symptomatic cases of CD, a positive screening test using endomysial or TG antibodies has a positive predictive value in the range of 97% to 100% for biopsy evidence of CD.[11,43] In contrast, in screening-identified CD, a positive test for TG or EMA has a much more variable positive predictive value for biopsy evidence of CD, often in the range of 80% to 100%.[6,13,44] Factors that influence the correlation between a positive screening test and histologic findings may include environmental factors such as recent dietary gluten content,[45] genetic factors such as dose effect of HLA-DQ2,DR3,[20] possible disease modifying non-HLA genes, the serologic test used,[46] and breastfeeding.[47]

In summary, we report data from a unique study that longitudinally evaluated an HLA-characterized general population cohort of children for the development of TG antibody seropositivity. The results suggest that celiac autoimmunity in screening-identified children is associated with statistically significant changes in measures of growth and nutrition and with subjective identification of symptoms by parents. Additional studies on routine screening of at-risk groups for evidence of CD are needed before evidence-based recommendations can be developed.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health Grants DK R01-DK50979, DK32493, DK32083, and M01RR00069; General Clinical Research Centers Program, National Center for Research Resources, Autoimmunity Center of Excellence Grant U19AI46374; Diabetes Endocrine Research Center Grant P3057516; and Autoimmunity Prevention Center Grant U19 AI 508864.

REFERENCES

1. Carlsson A, Axelsson I, Borulf S, Bredberg A, Ivarsson S-A. Serological screening for celiac disease in healthy 2.5-year-old children in Sweden. *Pediatrics.* 2001;107:42–45
2. Hoffenberg EJ, MacKenzie T, Barriga KJ, et al. A prospective study of the incidence of childhood celiac disease. *J Pediatr.* 2003;143:308–314
3. Catassi C, Ratsch I, Fabiani E, et al. High prevalence of undiagnosed coeliac disease in 5280 Italian students screened by antigliadin antibodies. *Acta Paediatr.* 1995;84:672–676
4. Not T, Horvath K, Hill I, et al. Celiac disease risk in USA: high prevalence of antiendomysium antibodies in healthy blood donors. *Scand J Gastroenterol.* 1998;33:494–498
5. Johnston S, Watson R, McMillan S, Sloan J, Love A. Prevalence of coeliac disease in Northern Ireland. *Lancet.* 1997;350:1370
6. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States. *Arch Intern Med.* 2003;163:286–292
7. Catassi C, Fabiani E, Ratsch I, et al. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr Suppl.* 1996;412:29–35
8. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology.* 2001;120:636–651
9. Revised criteria for diagnosis of coeliac disease. Report of working group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child.* 1990;65:909–911
10. When is a coeliac a coeliac? Report of a working group of the United European Gastroenterology Week in Amsterdam, 2001. *Eur J Gastroenterol Hepatol.* 2001;13:1123–1128
11. Troncone R, Maurano F, Rossi M, et al. IgA antibodies to tissue transglutaminase: an effective diagnostic test for celiac disease. *J Pediatr.* 1999;134:166–171
12. Dieterich W, Ehnis T, Bauer M, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med.* 1997;3:797–801
13. Hoffenberg EJ, Bao F, Eisenbarth GS, et al. Transglutaminase antibodies in children with a genetic risk for celiac disease. *J Pediatr.* 2000;137:356–360
14. Marsh M. Gluten, major histocompatibility complex, and the small intestine. *Gastroenterology.* 1992;102:330–354
15. Kemppainen T, Kroger H, Janatuinen E, et al. Osteoporosis in adult patients with celiac disease. *Bone.* 1999;24:249–255
16. Ferguson A, Kingstone K. Coeliac disease and malignancies. *Acta Paediatr.* 1996:85(suppl 412):78–81
17. Fabiani E, Taccari LM, Ratsch IM, Di Giuseppe S, Coppa GV, Catassi C. Compliance with gluten-free diet in adolescents with screening-detected celiac disease: a 5-year follow-up study. *J Pediatr.* 2000;136:841–843
18. Rewers M, Bugawan TL, Norris JM, et al. Newborn screening for HLA markers associated with IDDM: diabetes autoimmunity study in the young (DAISY). *Diabetologia.* 1996;39:807–812
19. *Census 2000 Redistricting Data (Public Law 94-171) Geographic Area: Denver County, Colorado.* Washington, DC: US Census Bureau; 2000
20. Bao F, Yu L, Babu S, et al. One third of HLA DQ2 homozygous patients with type 1 diabetes express celiac disease-associated transglutaminase autoantibodies. *J Autoimmun.* 1999;13:143–148
21. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data.* 2000;(314):1-27
22. de Onis M, Yip R, Mei Z. The development of MUAC-for-age reference data recommended by a WHO Expert Committee. *Bull World Health Organ.* 1997;75:11–18

23. Mei Z, Grummer-Strawn LM, de Onis M, Yip R. The development of a MUAC-for-height reference, including a comparison to other nutritional status screening indicators. *Bull World Health Organ.* 1997;75: 333–341
24. Bieri JG, Tolliver TJ, Catignani GL. Simultaneous determination of alpha-tocopherol and retinol in plasma or red cells by high pressure liquid chromatography. *Am J Clin Nutr.* 1979;32:2143–2149
25. Knight JA, Anderson S, Rawle JM. Chemical basis of the sulfo-phosphovanillin reaction for estimating total serum lipids. *Clin Chem.* 1972;18: 199–202
26. Horwitt MK, Harvey CC, Dahm CH Jr, Searcy MT. Relationship between tocopherol and serum lipid levels for determination of nutritional adequacy. *Ann N Y Acad Sci.* 1972;203:223–236
27. Smith JC Jr, Butrimovitz GP, Purdy WC. Direct measurement of zinc in plasma by atomic absorption spectroscopy. *Clin Chem.* 1979;25: 1487–1491
28. National Center for Health Statistics. *NHANES III Reference Manuals and Reports*. Hyattsville, MD: National Center for Health Statistics; 1996
29. Hill ID, Bhatnagar S, Cameron DJ, et al. Celiac disease: working group report of the first world congress of pediatric gastroenterology, hepatology, and nutrition. *J Pediatr Gastroenterol Nutr.* 2002;35(suppl 2): S78–S88
30. Catassi C, Fabiani E, Ratsch I, Coppa G, Giorgi P. Celiac disease in the general population: should we treat asymptomatic cases?*J Pediatr Gastroenterol Nutr.* 1997;24:S10–S13
31. Ionescu AA, Nixon LS, Evans WD, et al. Bone density, body composition, and inflammatory status in cystic fibrosis. *Am J Respir Crit Care Med.* 2000;162(suppl):789–794
32. Nilsen EM, Lundin KE, Krajci P, Scott H, Sollid LM, Brandtzaeg P. Gluten specific, HLA-DQ restricted T cells from coeliac mucosa produce cytokines with Th1 or Th0 profile dominated by interferon gamma. *Gut.* 1995;37:766–776
33. Monteleone G, Pender SL, Alstead E, et al. Role of interferon alpha in promoting T helper cell type 1 responses in the small intestine in coeliac disease. *Gut.* 2001;48:425–429
34. Salvati VM, MacDonald TT, Bajaj-Elliott M, et al. Interleukin 18 and associated markers of T helper cell type 1 activity in coeliac disease. *Gut.* 2002;50:186–190
35. Wieringa FT, Dijkhuizen MA, West CE, Northrop-Clewes CA, Muhilal. Estimation of the effect of the acute phase response on indicators of micronutrient status in Indonesian infants. *J Nutr.* 2002;132:3061–3066
36. Rea F, Polito C, Marotta A, et al. Restoration of body composition in celiac children after one year of gluten-free diet. *J Pediatr Gastroenterol Nutr.* 1996;23:408–412
37. American Gastroenterological Association medical position statement: celiac sprue. *Gastroenterology.* 2001;120:1522–1525
38. Fraser-Reynolds KA, Butzner JD, Stephure DK, Trussell RA, Scott RB. Use of immunoglobulin A-antiendomysial antibody to screen for celiac disease in North American children with type 1 diabetes. *Diabetes Care.* 1998;21:1985–1989
39. Acerini CL, Ahmed ML, Ross KM, Sullivan PB, Bird G, Dunger DB. Coeliac disease in children and adolescents with IDDM: clinical characteristics and response to gluten-free diet. *Diabet Med.* 1998;15: 38–44
40. Saukkonen T, Vaisanen S, Akerblom HK, Savilahti E. Coeliac disease in children and adolescents with type 1 diabetes: a study of growth, glycaemic control, and experiences of families. *Acta Paediatr.* 2002;91: 297–302
41. Westman E, Ambler GR, Royle M, Peat J, Chan A. Children with coeliac disease and insulin dependent diabetes mellitus–growth, diabetes control and dietary intake. *J Pediatr Endocrinol Metab.* 1999;12:433–442
42. Mariani P, Viti MG, Montuori M, et al. The gluten-free diet: a nutritional risk factor for adolescents with celiac disease? *J Pediatr Gastroenterol Nutr.* 1998;27:519–523
43. Lerner A, Kumar V, Iancu TC. Immunological diagnosis of childhood coeliac disease: comparison between antigliadin, antireticulin and antiendomysial antibodies. *Clin Exp Immunol.* 1994;95:78–82
44. Barera G, Bonfanti R, Viscardi M, et al. Occurrence of celiac disease after onset of type 1 diabetes: a 6-year prospective longitudinal study. *Pediatrics.* 2002;109:833–838
45. Murray J. The widening spectrum of celiac disease. *Am J Clin Nutr.* 1999;69:354–365
46. Stern M, Teuscher M, Wechmann T. Serological screening for coeliac disease: methodological standards and quality control. *Acta Paediatr.* 1996;85(suppl 412):49–51
47. Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against celiac disease. *Am J Clin Nutr.* 2002;75:914–921

UNFAIR PRICING DISPARITY

"Most major U.S. hospitals are required to set official 'charges' for their services, but then agree to discount or even ignore those charges when getting paid by big institutions such as insurance companies or the government. As a result, almost no one but uninsured individuals ever faces the official charges. . . . [I]n the case of hospitals, the pricing disparity isn't publicly known and falls most heavily on the vulnerable. America's 41 million people without health insurance tend to be young, working-class, and unaware that they are being billed more than everyone else for the same services."

Wall Street Journal. March 17, 2003

Submitted by Student

Clinical Features of Children With Screening-Identified Evidence of Celiac Disease

Edward J. Hoffenberg, Lisa M. Emery, Katherine J. Barriga, Fei Bao, Jennifer Taylor, George S. Eisenbarth, Joel E. Haas, Ronald J. Sokol, Iman Taki, Jill M. Norris and Marian Rewers

Pediatrics 2004;113;1254